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A highly stereoselective ether directed palladium catalysed aza-Claisen rearrangement†

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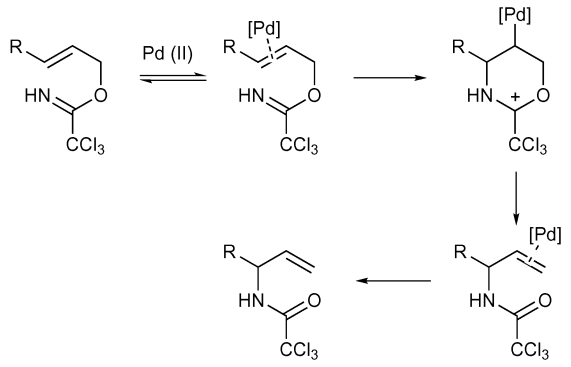
A highly stereoselective rearrangement of allylic trichloroacetimidates to allylic trichloroamides has been achieved using adjacent ether groups to direct facial coordination of the palladium(II) catalyst.

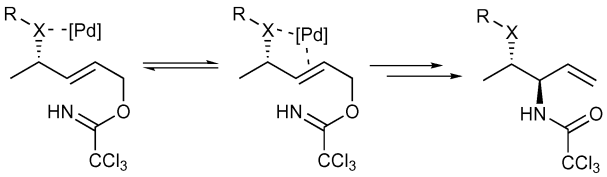
The thermal and metal-catalysed [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates to give allylic trichloroamides has found widespread use in synthetic organic chemistry.[1] Like other [3,3]-sigmatropic rearrangements, the reaction pathway progresses *via* a highly ordered chair-like transition state which allows the shift of stereochemical information from reactant to product.[1b] Moreover, the palladium(II) catalysed version of this reaction is carried out under extremely mild conditions allowing the isolation of products in high yields and excellent regio- and stereoselectivities.[1a,2] The metal catalysed reaction has been studied by the groups of Overman and Bosnich and shown to follow a stepwise pathway involving intramolecular amino palladation of the alkene followed by reductive elimination to generate the amide products (Scheme 1).[3]



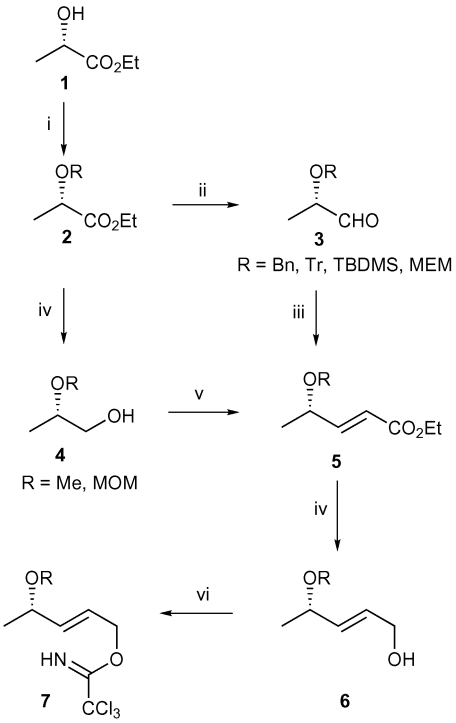
Scheme 1 Palladium catalysed aza-Claisen rearrangement.

More recently, efforts have focused on developing an asymmetric palladium(II) catalysed aza-Claisen reaction of trichloroacetimidates. The best results to date have been achieved by the Overman group using chiral palladium diamine complexes.[4] Following on from our previous work on chiral rearrangements[5] we envisaged a different approach involving the use of an adjacent chiral functional group to initially coordinate to the palladium catalyst and direct the metal intramolecularly to one face of the alkene resulting in a diastereoselective rearrangement (Scheme 2). We now report our preliminary investigations on the use of ether groups to direct, diastereoselective, palladium(II) catalysed rearrangements of allylic trichloroacetimidates.

In an effort to quantify the directing effect of different ether groups in such a rearrangement process, a series of allylic trichloroacetimidate substrates were synthesised (Scheme 3). Ether derivatives of (*S*)-ethyl lactate **1** were prepared using standard procedures,[6] and these were then converted into the corresponding aldehydes **3** using DIBAL-H. Subsequent reaction with triethyl phosphonoacetate under Horner–Wadsworth–Emmons (HWE) conditions yielded the *E*-allylic esters **5**, which were then reduced to the allylic alcohols **6** again using DIBAL-H as the reducing agent. Finally reaction with sodium hydride and trichloroacetonitrile using the Overman protocol[7] gave substrates **7** for the rearrangement reaction. Decomposition and volatility problems associated with the Me and MOM substituted aldehydes were overcome by reducing these compounds to the corresponding alcohols **4**. A one-pot, Swern oxidation–HWE reaction[8] gave the *E*-allylic esters and these were then converted into the desired Me and MOM ether allylic trichloroacetimidates in a similar manner.



Scheme 2 Directed aza-Claisen rearrangement.



Scheme 3 *Reagents and conditions*: i. see reference 6; ii. DIBAL-H (1.05 eq.), Et_2O, −78 °C; iii. triethyl phosphonoacetate, LiCl, DBU, MeCN; iv. DIBAL-H (2.2 eq.), Et_2O, −78 °C; v. DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C to RT, then triethyl phosphonoacetate, LiCl, DBU, yields of **6** from **1**, Bn (46%), Tr (62%), TBDMS (26%), Me (16%), MOM (34%), MEM (25%); vi. NaH, Cl_3CCN, 0 °C.

Allylic trichloroacetimidates **7** were subjected to rearrangement conditions using bis(acetonitrile)palladium(II) chloride as

† Electronic supplementary information (ESI) available: Experimental data and characterisation of compounds. See http://www.rsc.org/suppdata/ob/b5/b501346c/

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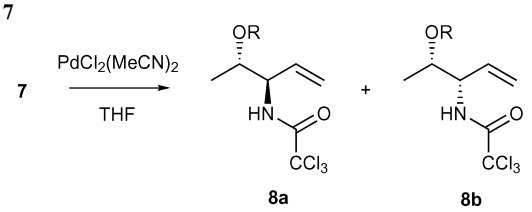
Table 1 Palladium(II) catalysed rearrangement of trichloroacetimidates **7**



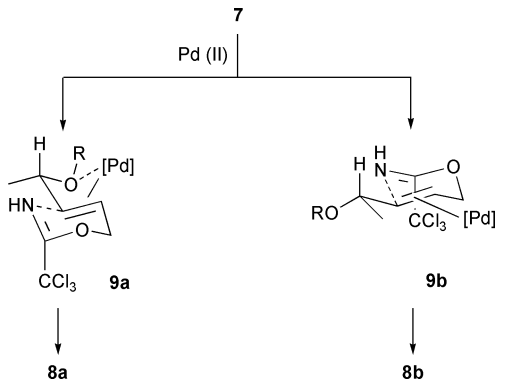
8a **8b**

Entry	R	Yield[a] (%)	Ratio[b] (**8a** : **8b**)
1	TBDMS	68%	2 : 1
2	Tr	70%	3 : 1
3	Bn	62%	3 : 1
4	Me	49%	7 : 1
5	MOM	64%	10 : 1
6	MEM	60%	8 : 1

[a] Isolated combined yields of **8a** and **8b** from allylic alcohol **6**. [b] Ratio in crude reaction mixture.

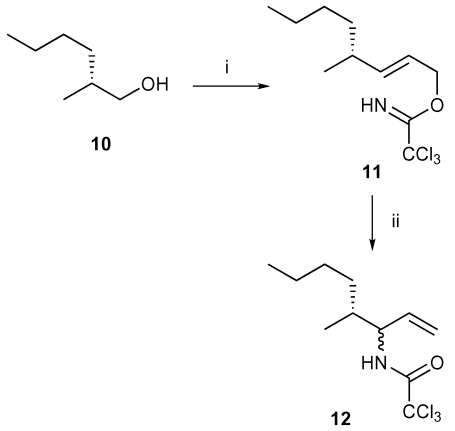
the catalyst. As expected, the bulky, sterically hindered ether groups (entries 1, 2, and 3) prevent efficient coordination to the palladium resulting in allylic trichloroamides **8a** and **8b** in low diastereoselectivity (Table 1).[9,10] However, switching to the much smaller methyl ether (entry 4) now allows effective coordination to the catalyst leading to a substantial increase in diastereoselectivity. This success prompted us to investigate whether additional oxygen atoms within the ether moiety could enhance this effect and indeed the use of the MOM group (entry 5) gave **8a** and **8b** in an excellent 10 : 1 ratio. Further enhancement with the MEM group (entry 6) was attempted and while the use of this group does lead to a highly selective rearrangement, no improvement on the MOM group was observed.

The stereochemistry of the major diastereomer can be explained if the reacting conformer is **9a**, which is formed initially by coordination of the palladium(II) metal centre to the ether oxygen (Scheme 4). This then directs the catalyst to the back face of the alkene, resulting in the allylic trichloroacetimidate adopting a chair-like conformation in which allylic 1,3 strain is minimized and where intramolecular attack can only take place from the front face of the alkene leading to the major diastereomer **8a**. The minor diastereomer **8b** is likely formed from reacting conformer **9b** where the catalyst coordinates directly to the least hindered, front face of the alkene forcing the rearrangement to proceed from the back face. Thus, for substrates containing bulky ether groups that cannot efficiently coordinate to the catalyst, this second pathway now becomes more competitive than for the smaller substrates leading to the observed, low diastereoselectivities.



Scheme 4 Reacting conformations that lead to the major and minor diastereomers.

These results strongly implicate the involvement of the ether oxygen atoms in directing facial coordination of the palladium catalyst to one face of the alkene resulting in a highly diastereoselective rearrangement. However, we sought further evidence and this was achieved by investigating the palladium catalysed rearrangement of a carbon analogue of the MOM ether substrate. Substrate **11** was synthesized from (2*R*)-2-methylhexanol[11] **10** in an analogous manner to that already described for the corresponding MOM compound (Scheme 5). Rearrangement of **11** using bis(acetonitrile)palladium(II) chloride gave the allylic trichloroamide product **12** in only a 2 : 1 ratio of diastereomers thereby confirming that the highly selective rearrangement observed for the Me, MOM and MEM ether substrates takes place *via* an ether directed process.



10 **11** **12**

Scheme 5 *Reagents and conditions*: i. a) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C to RT, then triethyl phosphonoacetate, LiCl, DBU, 34% over two steps, b) DIBAL-H (2.2 eq.), Et_2O, −78 °C, 45%, c) NaH, Cl_3CCN, 0 °C, 60%; ii, $PdCl_2(MeCN)_2$, THF, 59%.

In conclusion, we have demonstrated the use of ether groups to effectively direct facial coordination of palladium during the aza-Claisen rearrangement of allylic trichloroacetimidates resulting in a highly diastereoselective process. Further investigation of the use of other directing groups during rearrangements and the application of this process to natural product synthesis is currently underway.

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